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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	6

DATE MAILED: 10/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,243	TAYLOR, ALEXANDER H.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-31* is/are pending in the application.

4a) Of the above claim(s) *8-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1,5,5* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1, and 3-7 as accordingly amended and the species of Pan troglodytes in Paper No. 4 is acknowledged. The traversal is on the ground(s) that (1) the sequences in the original claims should remain grouped together as they were originally filed in the claims, (2) the framework regions I-III and IV should be grouped together as one invention (3) the sequences of the framework should be examined by species (see page 3 of response) and the search terms for one sequence in the group will necessarily be shared with another and the search of the sequences together would not be a undue burden (see page 4 of response). This is not found persuasive because as stated the frameworks are structurally distinct and each requires a separate search of each SEQ ID NO. In addition, the frameworks would not be a species election because they are distinct and art on one of the sequences would no t be art on the others. In addition the response suggests a new grouping of the claims (see page 5 of response). In response to this argument, the groupings stand as set forth in the restriction requirement. The proposed restriction requirement proposes to place polynucleotides and polypeptides together (see Groups V and VI) which as stated in the restriction requirement are patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 8-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic

or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 4.

3. Claims 1, 3-7 are under examination and will be examined to the extent the species of Pan troglodytes is the elected species of Old World apes.

Information Disclosure Statement

4. The IDS filed 7/16/01 has been considured, however, the PTO-1449 states page 1 of 2, however, only one page was found. If applicant intended to have 2 sheets them applicant should submit the second sheet with verified evidence that there were 2 sheets. Sheet 1 is included with this Office Action.

Specification

5. The disclosure is objected to because of the following informalities:

a. The specification contains embedded hyperlinks or other forms of browser executable code listed on page 9 and 12, for example, that is impermissible and requires deletion. The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. (see MPEP 608.01(p)).

b. The first line of the specification should be updated to indicate application 09./300970 is now abandoned.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 3-7 are indefinite for reciting "derived from" in claim 1 for the exact meaning of the phrase is not clear. It is not clear how the CDRs recited in claim 1 have been "derived from". Do the CDRs have changes in the amino acid residues than those in the parent non-human species? In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Claim 7 is indefinite for reciting "one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework" for the exact meaning of the phrase is not clear. It is not clear what framework residues are being replaced. In claim 1 the framework residues recited are residues from an old world ape. It is not clear if the framework residues that are solvent exposed are from the donor or the acceptor species. In addition, it is not clear how the framework is "homologous selected". Are the sequences of the donor compared in some way with the acceptor or are the framework residues of the non-human species compared with other non-human species sequences or are they

compared to the non-human primate? In addition it is not clear if the non-human primate is the old world ape.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibody comprising all 6 donor CDRs from an antigen specific donor antibody of a non-human species, wherein all 6 CDRs of the acceptor are replaced with the corresponding 6 CDRs of the donor, wherein the acceptor antibody is from Pan troglodyte, and wherein one or more CDR-contacting residues in the donor are retained and one or more solvent exposed framework residues in the donor are replaced with the corresponding residue in a Pan troglodyte acceptor framework, and wherein the antibody binds antigen, does not reasonably provide enablement for an antibody comprising any derived donor CDRs, wherein the CDRs can have deletions, replacements, or insertions from the amino acid sequence from the donor parent, from an antigen-specific antibody of a non-human species and acceptor framework residues from any non-human primate, wherein not all 6 CDRs of any non-human acceptor are replaced with the corresponding CDRs of the donor, and wherein the antibody does not bind antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working exampies, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody comprising any derived donor CDRs from an antigen-specific antibody of a non-human species and acceptor framework residues from any non-human primate, wherein not all 6 CDRs of any non-human acceptor are replaced with the corresponding CDRs of the donor, and wherein the antibody does not bind antigen.

The specification teaches antibodies comprising donor CDRs from (1) a rat anti-IL5 antibody (see pages 17-19, Example 5), (2) a murine anti-integrin antibody (see pages 19-21, Example 6), and (3) a murine anti-erythropoietin antibody (see pages 22-24), and acceptor frameworks from Pan troglodytes. All 6 CDRs from the acceptor were replaced with the corresponding CDRs of the donor. The specification teaches framework residues that can influence CDR presentation as well as CDR contacting residues. The specification teaches the transfer of the entire CDR of the donor, wherein no amino acid substitution, deletions, or insertions into the CDRs were made, to the acceptor. All three of the antibodies in the examples bind antigen. The specification fails to teach any other acceptor framework residues from any other non-human primate other than Pan troglodytes, wherein the antibody binds antigen. In addition, the specification does not teach altering the amino acid sequence of the CDRs of the donor.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The

amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody in unspecified order and transferred to any non-human framework sequence, have the required binding function. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Moreover, claims 1, 3-4 broadly encompass an antibody wherein only transfer of the CDRs are required. As evidenced by Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Therefore, in view of the lack of predictability in the art as evidenced by Rudikoff et al, Panka et al, and Amit et al, lack of guidance in the specification and in view of the

discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1, 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newman et al (U.S. Patent 5,756,096, filed 6/7/95) and further in view of Vijh-Warrier et al (Molecular Immunology 32:1081-1092, 1995, IDS #7) and Adair et al (WO 91/0996, published 7/11/91.

The claims are drawn to an antibody comprising donor CDRs derived from an antigen-specific donor antibody of a non-human species and acceptor framework residues derived from Pan troglodytes. Further embodiments include wherein one or more of the CDR-contacting residues are included, wherein the antibody comprises human constant region, wherein the solvent exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate.

Newman et al teach a primatized antibody comprising the variable domain from a monkey and the human igG1 constant region (see column 2, lines 1-10). Newman et al also teach the framework region can be from a chimpanzee (see column 2, line 9). Newman et al does not teach Pan troglodytes or replacement of one or more solvent exposed framework residues. These deficiencies are made up for in the teachings of Vijh-Warrier et al and Adair et al.

Vijh-Warrier et al teach the nucleotide and amino acid sequence of the variable region of a Pan troglodytes antibody (see abstract). Vijh-Warrier also teach several human germline variable region genes (see Figure 3, 4, and 5, and Table 1).

Adair et al teach methods of CDR grafting comprising acceptor framework and donor antigen binding regions (see abstract). Adair et al also teach non-CDR residues which contribute to antigen binding and CDR contacting residues (see pages 20-23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antibody comprising donor CDRs from a non-human species and acceptor framework residues from Pan troglodytes and further comprising human constant regions, wherein CDR-contacting residues in the donor are retained, wherein one or more solvent exposed framework residues are replaced with the corresponding residues selected from a non-human primate.

One of ordinary skill in the art would have been motivated to produce the claimed invention because Newman et al teach it has been postulated that non-human primate antibodies, e.g., chimpanzee monoclonal antibodies, to be tolerated in humans because they are structurally similar to human antibodies. (See column 1, lines 49-67). In addition, Newman et al teach "there are few if any differences in the amino acid sequence of the human and chimpanzee constant regions" (see column 4, lines 2-4)

and "framework are provided from another antibody, preferably a human or chimpanzee antibody" (see column 3, lines 38-40). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Vijh-Warrier et al teach "these findings suggest that chimpanzee mAbs are no more likely to elicit deleterious anti-immunoglobulin responses in humans than are human mAbs and emphasize the potential development of chimpanzee mAbs or chimpanzee-human chimeric mAbs for immunotherapeutic uses in humans" (see page 1089). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Adair et al teach donor CDRs from non-human species (see abstract and page 8, lines 3-7) and Adair et al teach a method comprising retaining residues that are involved with antigen binding or contacting the CDRs or replacing solvent exposed framework residues (see pages 20-23, 38-39, and Figure 3). Thus, it would have been prima facie obvious to have used the framework regions from a Pan troglodyte to produce the claimed antibody due to the high homology between human and Pan troglodytes immunoglobulin amino acid sequences and combine the teachings of Adair who has produced humanized antibodies with non-human CDRs and human frameworks.

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed antibodies because Vihj-Warrier et al teach high homology between Pan troglodytes and human immunoglobulin genes and Adair has produced humanized antibodies.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

12. No Claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3559. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.
703-306-5879